



CHALLENGES OF EU ACCESSION FOR DRUG REGULATION IN ROMANIA

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•INTRODUCTORY WORD

- **Modernisation of Romanian drug legislation started early in the '90 but its pace became faster with the official launch of negotiations for EU accession on February 15th 2000.**
- **The period since the official launch of negotiations in view of accession up to provisional closure on June 2nd 2003 of the "Free Movement of Goods" chapter, including the "Pharmaceuticals" subchapter, meant the actual conclusion of the transposition of the *Acquis communautaire* in the drug field such as it was at the beginning of 2003.**



2. PHARMACEUTICAL LEGISLATION

2.1. Present situation

The Romanian Pharmaceutical Law which is the Government Emergency Ordinance No 152/1999, approved with changes and completions through Law No 336/2002, with further changes and completions, transposes provisions of Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community code relating to medicinal products for human use.



2. PHARMACEUTICAL LEGISLATION

2.1. Present situation (ctd.)

The structure of the Romanian Pharmaceutical Law:

- CHAPTER I **General provisions; definitions**
- CHAPTER II **Marketing authorization of medicinal products**
- CHAPTER III **Manufacture of medicinal products**
- CHAPTER IV **Distribution of medicinal products**
- CHAPTER V **Surveillance of medicinal products**
- CHAPTER VI **Testing of medicinal products**
- CHAPTER VII **Special provisions for toxic and narcotic medicinal products**
- CHAPTER VIII **Import and export of medicinal products**
- CHAPTER IX **Price of medicinal products**
- CHAPTER X **Sanctions**
- CHAPTER XI **Final provisions**



2. PHARMACEUTICAL LEGISLATION

2.1. Present situation (ctd.)

- **The Romanian Pharmaceutical Law relies on all the principles of Directive 2001/83/EC, which are further detailed in Regulations approved through Minister of Health Orders.**
- **It has become well known fact that European legislation in general and drug legislation in particular are subject to ongoing change, which is why national legislation of members and candidate states alike share the same tendency. The already sock phrase related to change of European legislation is that "transposition of the *Acquis communautaire*" is a moving target.**



2. PHARMACEUTICAL LEGISLATION

2.1. Present situation (ctd.)

In that context, following provisional closure by Romania of the Chapter “Free Movement of Goods”, the process concerning transposition into Romanian drug legislation of newly emerging provisions of European legislation has been ongoing with every new change in European Directives.



2. PHARMACEUTICAL LEGISLATION

2.1. Present situation (ctd.)

In addition to Directive 2001/83/EC, Romania has transposed other European Directives & Regulations:

- **Commission Regulations No 141/2000 and 847/2000 on orphan medicinal products, mainly transposed for the purpose of making medical professionals become familiar with this comparatively new issue in Romania;**
- **Commission Regulations No 1084/2003 and 1085/2003 on variations, transposed for practical needs as current working tool for both applicants and the NMA;**
- **Directive 2001/20/EC on clinical trials and its implementation guidelines, also used in current activity in the field of clinical trials in Romania.**



2. PHARMACEUTICAL LEGISLATION

2.2. Issues to be solved during Pre-Accession

Taking into account that EU pharmaceutical legislation has been revised and new directives have emerged modifying Directive 2001/83/ CE, setting October 30th 2005 as deadline for its transposition into national legislations of member states, Romania has expressed its commitment to revise the current Drug Law, the revised form about to come into force at the end of 2005 at the latest.



2. PHARMACEUTICAL LEGISLATION

2.2. Issues to be solved during Pre-Accession (ctd.)

The 4 directives to be considered in the process related to revision of the Drug Law are:

- Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC**
- Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.**



2. PHARMACEUTICAL LEGISLATION

2.2. Issues to be solved during Pre-Accession (ctd.)

- **Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC of European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use**
- **Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC of European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.**



2. PHARMACEUTICAL LEGISLATION

2.2. Issues to be solved during Pre-Accession (ctd.)

Revision will be undertaken not only of the Drug Law but also of the entire bulk of regulations derived from the law, approved through Orders of the Minister of Health, so that, by 2006, the entire drug manufacturing, authorisation and surveillance activity carried out in Romania shall be in line with provisions of the new legislation.



2. PHARMACEUTICAL LEGISLATION

2.2. Issues to be solved during Pre-Accession (ctd.)

The main changes brought about by the new European legislation, to be included into the emerging Romanian Drug Law are:

- **Generic definition, such as provided for in art. 10.2(b) of Directive 2001/83: “a generic medicinal product is a medicinal product which has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies”**



2. PHARMACEUTICAL LEGISLATION

2.2. Issues to be solved during Pre-Accession (ctd.)

- ***same active substance*** which means the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in regards of safety and/or efficacy



2. PHARMACEUTICAL LEGISLATION

2.2. Issues to be solved during Pre-Accession (ctd.)

- *same pharmaceutical form* which means the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form



2. PHARMACEUTICAL LEGISLATION

2.2. Issues to be solved during Pre-Accession (ctd.)

- ***exemption from presenting bioavailability studies:*** bioavailability studies need not be required of applicants if they can demonstrate that the generic medicinal product meets relevant criteria as defined in the appropriate guideline



2. PHARMACEUTICAL LEGISLATION

2.2. Issues to be solved during Pre-Accession (ctd.)

-Data exclusivity issues:

- **8+2+1 formula for all products - in line with art. 10.1 of Directive 2001/83**
- **Data exclusivity on new indications for WEU substance – in line with art. 10.5 of Directive 2001/83**
- **Data exclusivity on OTC switch - in line with art. 74a of Directive 2001/83**



2. PHARMACEUTICAL LEGISLATION

2.2. Issues to be solved during Pre-Accession (ctd.)

-European Reference Product - according to art. 10.1 of Directive 2001/83

-Bolar provision - according to art. 10.6 of Directive 2001/83

-One five – year renewal - according to provisions of art. 24 (2) and (3) of Directive 2001/83



2. PHARMACEUTICAL LEGISLATION

2.2. Issues to be solved during Pre-Accession (ctd.)

-Sunset clause for marketing authorization - according to provisions of art. 24 (4) (any authorization which within 3 years of its granting is not followed by the actual placing on the market of the authorized product in Romania, shall cease to be valid) and (5) (when an authorized product previously placed on the market in Romania is no longer actually present on the market for a period of 3 consecutive years, the authorization for that product shall cease to be valid) of Directive 2001/83



2. PHARMACEUTICAL LEGISLATION

2.2. Issues to be solved during Pre-Accession (ctd.)

-Format and content of the manufacturing authorization, inspection reports and certificate of good manufacturing practice in line with European guidelines - according to provisions of art. 47 and 111 of Directive 2001/83



3. DATA EXCLUSIVITY

3.1. Current status

The issues of data exclusivity was initially regulated starting with 2001, by 2 decisions of the NMA Scientific Council and then included into the Romanian Drug Law in April 2004, under the form provided for in the initial version of the Directive 2001/83/CE: 6 years (for ordinary chemical entities) and 10 years for « high-technology medicinal products », the exclusivity period starting from the date of the original medicinal product authorisation in the EU or country of origin.



3. DATA EXCLUSIVITY

3.1. Current status (ctd.)

Application of law provisions is outlined in Minister of Health Order No 1443/2003. The same Order explains the phrase « high-technology medicinal products » specified in the law. The source for this explanation had been types of drugs as included in lists A and B of Council Regulation No 2309/93/EEC of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal products:



3. DATA EXCLUSIVITY

3.1. Current status (ctd.)

a) Medicinal products developed by means of one of the following biotechnological processes:

- **Recombinant DNA technologies**
- **Controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells**
- **Hybridoma and monoclonal antibody methods**



3. DATA EXCLUSIVITY

3.1. Current status (ctd.)

- **Medicinal products developed by biotechnological processes other than those mentioned under a) and which constitute a significant innovation**
- **Medicinal products administered by means of new delivery systems which constitute a significant innovation**
- **Medicinal products presented for an entirely new indication which is of significant therapeutic interest**



3. DATA EXCLUSIVITY

3.1. Current status (ctd.)

- **Medicinal products based on radio-isotopes which are of significant therapeutic interest**
- **New medicinal products derived from human blood or human plasma**
- **Medicinal products the manufacture of which employs processes which demonstrate a significant technical advance such as two-dimensional electrophoresis under micro-gravity**
- **Medicinal products containing a new active substance which, on the date of entry into force of the Minister of Health Order, was not authorized by Romania or by any EU member states**



3. DATA EXCLUSIVITY

3.2. Issues to be solved during Pre-Accession

Under the revised Drug Law provisions, to come into force by the end of 2005, issues related to data exclusivity will be taken over as provided in the new European legislation, under TITLE III "PLACING ON THE MARKET", CHAPTER 1 "Marketing authorization", Article 10, i.e.:

- 8+2+1 formula for all products, meaning that:**
- a generic application for a reference medicinal product which is or has been authorized for not less than 8 years in Romania, a member state or in the Community can be submitted**



3. DATA EXCLUSIVITY

3.2. Issues to be solved during Pre-Accession (ctd.)

- a generic medicinal product authorized pursuant to this provision shall not be placed on the market until **10 years** have elapsed from the initial authorization of the reference product

- the ten-year period shall be extended to a maximum of **1 year** if, during the first 8 years of those **10 years**, the marketing authorization holder obtains an authorization for one or more new therapeutic indications, which, during the scientific evaluation prior their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.



3. DATA EXCLUSIVITY

3.2. Issues to be solved during Pre-Accession (ctd.)

Data exclusivity on new indications for WEU substances

Where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical and clinical studies were carried out in relation to the new indication



3. DATA EXCLUSIVITY

3.2. Issues to be solved during Pre-Accession (ctd.)

Data exclusivity on OTC switch

Where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized.



3. DATA EXCLUSIVITY

3.2. Issues to be solved during Pre-Accession (ctd.)

New provisions concerning the 8+2+1 formula on data exclusivity shall not apply to medicinal products for which an application for authorization has been submitted before the date of entry into force of the Law (according to provisions under TITLE XIV "FINAL PROVISIONS" of the consolidated form of the Directive 2001/83/EC).



4. SPC

The Romanian Law on the Supplementary Protection Certificate for Medicinal and Phytosanitary Products elaborated by the Patent Office in accordance with the Council Regulation No 1768/92 of 18 June 1992, concerning the creation of a supplementary protection certificate for medicinal products and Regulation 1510/96 of the European Parliament and of the Council of 23 July 1996 concerning the creation of supplementary protection certificate for plant protection products has been approved by the Parliament and is about to be passed by the Romanian President in the near future.

The law will enter into force upon accession into the EU.



5. UPDATE OF THE EXISTING DOSSIERS

5.1. Current status

Since 2000, it has been constant NMA concern to approve for marketing authorisation just products whose documentation was in line with the European legislation in force.

The initial provisions related to the content of authorisation files were included in Regulations on marketing authorization and surveillance of medicinal products for human use approved through NMA Scientific Council Decision No 27/06.10.2000.

Then, these Regulations were revised and a new version was approved through NMA Scientific Council Decision No 1/17.01.2003.

Both versions were in line with European legislation in force at the time of their approval.



5. UPDATE OF THE EXISTING DOSSIERS

5.1. Current status (ctd.)

Special NMA Scientific Council decisions on the update of the authorization documents have also been approved such as:

- NMA Scientific Council Decision No 22/5 October 2001 on the approval of Regulations concerning the acceptance of the authorization documentation in CTD format**

- NMA Scientific Council Decision No 4/17 January 2003 on the approval of Regulations concerning handling of authorization documentation sent by the applicants for “old medicinal products” in order to update their authorization documentation**

Reception and evaluation of applications submitted to the NMA after coming into force of regulations mentioned above took into account their requests, thus insuring marketing authorisation in Romania of drugs on the basis of authorisation documentation in line with requests of European legislation.



5. UPDATE OF THE EXISTING DOSSIERS

5.2. Issues to be solved during Pre-Accession

NMA will set up guidelines concerning requests for documentation update including more detailed provisions than those included into NMA Scientific Council Decision No 4/17 January 2003, taking into account experience in the field of countries that were included in the EU in the first wave.

NMA Scientific Council will set up a Decision on the deadline for acceptance of documentation on CTD exclusively.



6. BOLAR PROVISIONS

6.1. Current status

Legislation in force on IP Protection:

- **Patents Law No 64/1991 with further modifications and completions**
- **Government Decision No 499/2003 for the approval of the Regulations on the application of the Law No 64/1991**

is harmonized with international standards.



6. BOLAR PROVISIONS

6.1. Current status (ctd.)

Art.35, letter c) of Chapter IV “Rights and Obligations” of the Patents Law No 64/1991 with further modifications and completions specifies that manufacturing or use of the invention to non-trade purposes does not represent infringement of the owner’s right.



6. BOLAR PROVISIONS

6.1. Current status (ctd.)

Rule 68 – “Exceptions from Rights Infringement” of Chapter IV “Rights” of Government Decision No 499/2003 for the approval of Regulations on the application of Law No 64/1991 mentions the following under par. (1), letter a): “acts preceding registration of a drug as provided by national drug legislation are no infringement of rights as issued from a patent for a drug, on condition the marketing authorisation issued by the lawful institution is only applicable after expiry date of patent validity.”



6. BOLAR PROVISIONS

6.1. Current status (ctd.)

Based on these provisions, research has been carried out in Romania in view of preparation of authorisation documentation and applications for authorisation have been submitted to the NMA for generic products before expiry of patent validity.



6. BOLAR PROVISIONS

6.2. Issues to be solved during Pre-Accession

The new drug legislation will take over the Bolar provisions as specified in art. 10.6 of Directive 2001/83:

“Conducting the necessary studies and trials with the view to the application of the paragraphs 1, 2, 3 and 4 (authorization of generic medicinal products) and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products”.



7. TRANSITIONAL MEASURES

Romania has not negotiated transition periods for the pharmaceutical sector because, in view of achievements so far (update of documentation, GMP implementation, NMA staff training), the Romanian pharmaceutical sector has been deemed fit to implement all requests of European legislation before the moment of accession.



8. CHALLENGES FOR NMA DURING THE PRE-ACCESSION PERIOD

During pre-accession, NMA will reinforce achievements so far and make its best to improve its activity through:

- **Active participation of NMA representatives as observers in EMEA and EC working groups, thus insuring familiarisation of Romanian specialists with European procedures and practices and smooth integration into the European system after accession;**



8. CHALLENGES FOR NMA DURING THE PRE-ACCESSION PERIOD (ctd)

- Reinforced collaboration and experience exchange with similar institutions in EU Member States;**
- Increased involvement of NMA representatives in activities of the European Pharmacopoeia Commission, in the new quality as full membership granted in September 2003 in result of Romania's accession to the Convention for the European Pharmacopoeia as well as GMP inspection activities organised by PIC/S.**



8. CHALLENGES FOR NMA DURING THE PRE-ACCESSION PERIOD (ctd)

- Reinforced activity carried out by NMA Control Departments in the Official Medicines Control Laboratories (OMCL) network and setting up in NMA of excellence centres for certain control methods;**
- Adjustment of NMA informational system for rendering it compatible with the European system;**
- Permanent improvement of MNA system for quality management and participation to benchmarking activities;**
- Improved communication with interested parties and insurance of transparency of its activities.**



9. CONCLUSIONS

On the 1st January 2007, the Romanian Pharmaceutical Sector will have acquired all tools required for its integration into the European system:

- Legislation harmonised to European legislation;**
- Pharmaceutical industry ready for competition on the European market;**
- Competent drug authority able to cope with operation in the European system through appropriate institutional structure, adequate equipment and well trained and motivated staff.**